PATENT COOPERATION TREATY

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

(Chapter II of the Patent Cooperation Treaty)

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference TR010PCT	**FOR FURTHER ACTION**	See Form PCT/IPEA/416
International application No. PCT/JP2004/004385	International filing date *(day/month/year)* 26.03.2004	Priority date *(day/month/year)* 28.03.2003

International Patent Classification (IPC) or national classification and IPC
C07K7/08, A61K38/10, C12N15/11, G01N33/50, C12N15/62, A01K67/027, C12N15/10, A61P25/28

Applicant
INTELLECTUAL PROPERTY CONSULTING INC. et al.

1. This report is the international preliminary examination report, established by this International Preliminary Examining Authority under Article 35 and transmitted to the applicant according to Article 36.
2. This REPORT consists of a total of 11 sheets, including this cover sheet.
3. This report is also accompanied by ANNEXES, comprising:
   a. ☐ *sent to the applicant and to the International Bureau)* a total of sheets, as follows:
      ☐ sheets of the description, claims and/or drawings which have been amended and are the basis of this report and/or sheets containing rectifications authorized by this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions).
      ☐ sheets which supersede earlier sheets, but which this Authority considers contain an amendment that goes beyond the disclosure in the international application as filed, as indicated in item 4 of Box No. I and the Supplemental Box.
   b. ☐ *(sent to the International Bureau only)* a total of (indicate type and number of electronic carrier(s)) , containing a sequence listing and/or tables related thereto, in computer readable form only, as indicated in the Supplemental Box Relating to Sequence Listing (see Section 802 of the Administrative Instructions).

4. This report contains indications relating to the following items:

☒	Box No. I	Basis of the opinion
☐	Box No. II	Priority
☒	Box No. III	Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
☒	Box No. IV	Lack of unity of invention
☒	Box No. V	Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
☒	Box No. VI	Certain documents cited
☐	Box No. VII	Certain defects in the international application
☐	Box No. VIII	Certain observations on the international application

Date of submission of the demand	Date of completion of this report
22.10.2004	04.07.2005

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INTERNATIONAL PRELIMINARY REPORT ON PATENTABILITY

International application No.
PCT/JP2004/004385

Box No. I Basis of the report

1. With regard to the **language**, this report is based on the international application in the language in which it was filed, unless otherwise indicated under this item.

   ☐ This report is based on translations from the original language into the following language , which is the language of a translation furnished for the purposes of:
   - ☐ international search (under Rules 12.3 and 23.1(b))
   - ☐ publication of the international application (under Rule 12.4)
   - ☐ international preliminary examination (under Rules 55.2 and/or 55.3)

2. With regard to the **elements*** of the international application, this report is based on *(replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report)*:

   Description, Pages

   1-433 as originally filed

   Claims, Numbers

   1-115 as originally filed

   Drawings, Sheets

   1/27-27/27 as originally filed

   ☒ a sequence listing and/or any related table(s) - see Supplemental Box Relating to Sequence Listing

3. ☐ The amendments have resulted in the cancellation of:
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

4. ☐ This report has been established as if (some of) the amendments annexed to this report and listed below had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).
   - ☐ the description, pages
   - ☐ the claims, Nos.
   - ☐ the drawings, sheets/figs
   - ☐ the sequence listing *(specify)*:
   - ☐ any table(s) related to sequence listing *(specify)*:

* *If item 4 applies, some or all of these sheets may be marked "superseded."*

Box No. III Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

1. The questions whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 11-40, 41-48 (part), 49, 50-58 (part), 59, 60-61 (part), 62-65, 66 (part), 67-71, 72-74 (part), 75 (part), 76-79, 80 (part), 81-85, 86-88 (part), 89 (part), 90, 91-92 (part), 97-115 (part); 99-104, 108 (industrial applicability)

because:

☒ the said international application, or the said claims Nos. 99-104, 108 (industrial applicability) relate to the following subject matter which does not require an international preliminary examination (specify):

see separate sheet

☐ the description, claims or drawings *(indicate particular elements below)* or said claims Nos. are so unclear that no meaningful opinion could be formed *(specify)*:

☐ the claims, or said claims Nos. are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for the said claims Nos. 11-40, 41-48 (part), 49, 50-58 (part), 59, 60-61 (part), 62-65, 66 (part), 67-71, 72-74 (part), 75 (part), 76-79, 80 (part), 81-85, 86-88 (part), 89 (part), 90, 91-92 (part), 97-115 (part)

☐ the nucleotide and/or amino acid sequence listing does not comply with the standard provided for in Annex C of the Administrative Instructions in that:

the written form	☐	has not been furnished
	☐	does not comply with the standard
the computer readable form	☐	has not been furnished
	☐	does not comply with the standard

☐ the tables related to the nucleotide and/or amino acid sequence listing, if in computer readable form only, do not comply with the technical requirements provided for in Annex C-*bis* of the Administrative Instructions.

☐ See separate sheet for further details

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Box No. IV Lack of unity of invention

1. ☒ In response to the invitation to restrict or pay additional fees, the applicant has:
   - ☐ restricted the claims.
   - ☐ paid additional fees.
   - ☐ paid additional fees under protest.
   - ☒ neither restricted nor paid additional fees.

2. ☐ This Authority found that the requirement of unity of invention is not complied with and chose, according to Rule 68.1, not to invite the applicant to restrict or pay additional fees.

3. This Authority considers that the requirement of unity of invention in accordance with Rules 13.1, 13.2 and 13.3 is

   ☐ complied with.

   ☒ not complied with for the following reasons:

   see separate sheet

4. Consequently, this report has been established in respect of the following parts of the international application:

   ☐ all parts.

   ☒ the parts relating to claims Nos. 1-10, 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-74 (part), 75 (part), 80 (part), 86-88 (part), 89 (part), 91 (part), 92 (part), 93, 97-115 (part) .

Box No. V Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. Statement

Novelty (N)	Yes:	Claims	5-10, 41-48, 50-58, 60, 74, 88, 99, 103-104, 108-114
	No:	Claims	1-4, 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97, 98, 100-102, 105-107, 115
Inventive step (IS)	Yes:	Claims	-
	No:	Claims	1-10, 41-48, 50-58, 60-61, 66, 72-74, 75, 80, 86-88, 89, 91, 92, 93, 97-115
Industrial applicability (IA)	Yes:	Claims	claims 99-104, 108 see separate sheet
	No:	Claims	-

2. Citations and explanations (Rule 70.7):

   see separate sheet

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Box No. VI Certain documents cited

1. Certain published documents (Rule 70.10)

   and / or

2. Non-written disclosures (Rule 70.9)

   see separate sheet

Supplemental Box relating to Sequence Listing

Continuation of Box I, item 2:

1. With regard to any **nucleotide and/or amino acid sequence** disclosed in the international application and necessary to the claimed invention, this report has been established on the basis of:

   a. type of material:

   ☒ a sequence listing

   ☐ table(s) related to the sequence listing

   b. format of material:

   ☒ in written format

   ☐ in computer readable form

   c. time of filing/furnishing:

   ☒ contained in the international application as filed

   ☒ filed together with the international application in computer readable form

   ☐ furnished subsequently to this Authority for the purposes of search and/or examination

   ☐ received by this Authority as an amendment on

2. ☐ In addition, in the case that more than one version or copy of a sequence listing and/or table(s) relating thereto has been filed or furnished, the required statements that the information in the subsequent or additional copies is identical to that in the application as filed or does not go beyond the application as filed, as appropriate, were furnished.

3. Additional observations, if necessary:

Re Item III.

1- Claims 99-104,108 relate to subject-matter considered by this Authority to be covered by the provisions of Rule 67.1(iv) PCT. Consequently, no opinion will be formulated with respect to the industrial applicability of the subject-matter of these claims (Article 34(4)(a)(I) PCT).

Re Item IV.

2- The separate inventions/groups of inventions are:

Invention 1:
Claims 1-10, 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-74 (part), 75 (part), 80 (part), 86-88 (part), 89 (part), 91 (part), 92 (part), 93, 97-115 (part)
A composition for regenerating nerves comprising an agent capable of specifically interacting with a p75 polypeptide or capable of modulating p75.

Invention 2:
Claims 11-20, 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-74 (part), 75 (part), 80 (part), 86-89 (part), 91-92 (part), 97-115 (part)
A composition for regenerating nerves, comprising an agent capable of specifically interacting with a Rho GDI polypeptide, or capable of modulating Rho GDI.

Invention 3:
Claims 21-30, 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-75 (part), 80 (part), 86-89 (part), 91 (part), 92 (part), 97-115 (part)
A composition for regenerating nerves, comprising an agent capable of specifically interacting with a Rho polypeptide, or capable of modulating Rho.

Invention 4:
Claims 31-40, 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-75 (part), 80 (part), 86-89 (part), 91-92 (part), 97-115 (part)
A composition for regenerating nerves, comprising an agent capable of specifically interact with a Rho kinase polypeptide or capable of modulating Rho kinase.

Invention 5:
Claims 41-48 (part), 50-58 (part), 60 (part), 61 (part), 62-63 (part), 64, 66 (part), 68

(part), 70, 72-74 (part), 75-77 (part), 78, 80 (part), 82 (part), 84, 86-88 (part), 89 (part), 90-92 (part), 94 (part), 97-115 (part)
A composition for regenerating nerves comprising an agent capable of specifically interacting with PKC or capable of modulating PKC.

Invention 6:
Claims 41-48 (part), 50-58 (part), 60 (part), 61 (part), 62-63 (part), 65, 66 (part), 68 (part), 69, 71, 72-74 (part), 75-77 (part), 79, 80 (part), 82 (part), 85, 86-88 (part), 89 (part), 90-92 (part), 94 (part), 97-115 (part)
A composition for regenerating nerves comprising an agent capable of interacting with IP3 or capable of modulating IP3.

Invention 7:
Claims 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 67, 68 (part), 72-74 (part), 75 (part), 80 (part), 81, 82 (part), 86-88 (part), 89 (part), 91-92 (part), 97-115 (part)
A composition for regenerating nerves, comprising an agent capable of specifically interacting with RhoA or capable of modulating RhoA.

Invention 8:
Claims 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-74 (part), 75 (part), 80 (part), 86-88 (part), 89 (part), 91 (part), 92 (part)part), 97-115 (part)
A composition for regenerating nerves comprising an agent capable of modulating MAG.

Invention 9:
Claims 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-74 (part), 75 (part), 80 (part), 86-88 (part), 89 (part), 91 (part), 92 (part)part), 97-115 (part)
A composition for regenerating nerves comprising an agent capable of modulating GT1b.

Invention 10:
Claims 41-48 (part), 50-58 (part), 60 (part), 61 (part), 66 (part), 72-74 (part), 75 (part), 80 (part), 86-88 (part), 89 (part), 91 (part), 92 (part)part), 95, 96, 97-115 (part)
A composition for regenerating nerves comprising an agent capable of modulating p21.

2.1- Inventions 1-10 are not so linked as to form a single general inventive concept

(Rule 13.1 PCT) for the following reasons:

The present application is concerned with compositions for regenerating nerves comprising either:

1: an agent capable of specifically interacting with a p75 polypeptide or capable of modulating p75,
2: an agent capable of specifically interacting with a Rho GDI polypeptide or capable of modulating Rho GDI,
3: an agent capable of specifically interacting with a Rho polypeptide or capable of modulating Rho,
4: an agent capable of specifically interacting with a Rho kinase polypeptide or capable of modulating Rho kinase,
5: an agent capable of specifically interacting with PKC or capable of modulating PKC,
6: an agent capable of specifically interacting with IP3 or capable of modulating IP3,
7: an agent capable of specifically interacting with RhoA or capable of modulating RhoA,
8: an agent capable of modulating MAG,
9: an agent capable of modulating GT1b, or
10: an agent capable of modulating p21.

The problem posed in the present application can be seen as the promotion of nerve regeneration.
The solution proposed in the present application is to disrupt the p75 signalling pathway, by providing any of the agents 1-10, as listed above.

The mere fact of participating in the same p75 signalling pathway does not confer a unitary character to the 10 therapeutic targets listed above. These therapeutic targets do neither share a common structure or nor a common activity.

The number and type of agents capable of specifically interacting or of modulating these different targets is very diverse and is not linked by any common feature in terms of structure and / or activity and / or pharmacological properties.

Finally, it is well known (see D4, D5, D6, D7, D8 and / or D9) that p75 activation inhibits nerve regeneration in vivo and that by disrupting p75 activation, nerve regeneration can be promoted.
For that purpose, an antibody against p75 is disclosed in D4, KGK or KGA are

used in D5 and a p75 antisense is provided in D9.
Furthermore, D2 mentions pep5 ("CFFEGGFFNHNPRYC"), which interacts with the intracellular "death domain" of p75.

Hence, if any, the only common concept which could be seen as linking the agents 1-10 is neither novel, nor inventive.

2.2- Hence, only invention 1 has been searched and is the subject of the present opinion.

Re Item V.

3- The following documents are referred to in this communication:

D1 : ILAG L L ET AL: "Selection of a peptide ligand to the p75 neurotrophin receptor death domain and determination of its binding sites by NMR." BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS. 5 FEB 1999, vol. 255, no. 1, 5 February 1999 (1999-02-05), pages 104-109, XP002295643 ISSN: 0006-291X

D2 : ILAG, LEOPOLD LUNA: "biochemical and biophysical aspects of molecular recognition and signalling by neurotrophins" DOKTORSAVHANDLING VID KAROLINSKA INSTITUET, [Online] 7 November 1997 (1997-11-07), XP002295644 Retrieved from the Internet: URL:http://diss.kib.ki.se/197/19971107ilag />; [retrieved on 2004-09-09]

D3 : WONG SCOTT T ET AL: "A p75(NTR) and Nogo receptor complex mediates repulsive signaling by myelin-associated glycoprotein." NATURE NEUROSCIENCE. DEC 2002, vol. 5, no. 12, December 2002 (2002-12), pages 1302-1308, XP002295645 ISSN: 1097-6256

D4 : US 6 242 416 B1 (GILCHREST BARBARA A ET AL) 5 June 2001 (2001-06-05)

D5 : YAMASHITA TOSHIHIDE ET AL: "The p75 receptor transduces the signal from myelin-associated glycoprotein to Rho." THE JOURNAL OF CELL BIOLOGY. 13 MAY 2002, vol. 157, no. 4, 13 May 2002 (2002-05-13), pages 565-570, XP002295646 ISSN: 0021-9525

D6 : WANG KEVIN C ET AL: "P75 interacts with the Nogo receptor as a co-receptor for Nogo, MAG and Omgp." NATURE. 7 NOV 2002, vol. 420, no. 6911, 7 November 2002 (2002-11-07), pages 74-78, XP001183135 ISSN: 0028-0836

D7 : WO 95/11253 A (BARRETT GRAHAM LESLIE ; INST MEDICAL W &; E HALL

(AU)) 27 April 1995 (1995-04-27)

3.1- The relevant passages are those indicated in the search report, unless otherwise specified.

NOVELTY - Art. 33 (1) and (2) PCT

4- Claims 1-4, 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97, 98, 100-102, 105-107 lack novelty

Note: A composition is only defined by its components and not by its intended use or alleged effects.

4.1- D2 discloses pep5, and is hence novelty destroying for the subject matter of claims 1-4, 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97, 98, 100-102, 105-107.

4.2- D3 is also novelty destroying for the subject matter of claims 1-4, 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97, 98, 100-102, 105-107.

4.3- D4 mentions that the association of NgR with p75 can be disrupted by an antibody against p75. D4 is novelty destroying for the subject matter of claims 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97-98, 100-102, 105-107.

4.4- D5 discloses the inhibition of the activation of p75 by beta-amyloid protein. D5 is novelty destroying for the subject matter of claims 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97-98, 100-102, 105-107.

4.5- D9 (p75 antisenses for the same purpose as in the present application) is novelty destroying for the subject matter of claims 61, 66, 72, 73, 75, 80, 86, 87, 89, 91-93, 97-98, 100-102, 105-107.

4.6- D10 is novelty destroying for the subject matter of claim 115.

INVENTIVE STEP - Art. 33 (1) and (3) PCT

5- Claims 1-10, 41-48, 50-58, 60-61, 66, 72-74, 75, 80, 86-88, 89, 91, 92, 93, 97-115 lack inventive step:

5.1- Should novelty be established, which does not appear to be the case (see above), then the subject matter claimed in the present application would still not be considered as being inventive, in view of D2 or D3, taken alone or in combination with any of D4, D5, D7, D8, D9 or D10.

5.2- The features of claims 5,10,41-48,50-58 are merely one of several straightforward possibilities from which the skilled person would select, in accordance with circumstances, without the exercise of inventive skill, in order to solve the problem posed, in particular in view of D11 or D12.

5.3- No inventive step can hence be acknowledged.

INDUSTRIAL APPLICABILITY - Art. 33 (1) and (4) PCT

6- For the assessment of the present claims 99-104,108 on the question whether they are industrially applicable, no unified criteria exist in the PCT Contracting States. The patentability can also be dependent upon the formulation of the claims. The EPO, for example, does not recognize as industrially applicable the subject-matter of claims to the use of a compound in medical treatment, but may allow, however, claims to a known compound for first use in medical treatment and the use of such a compound for the manufacture of a medicament for a new medical treatment.

7- Any amendment should be accompanied by a precise indication of the source / support in the originally filed disclosure otherwise the IPER may be drafted on the non amended version only.